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10/019,954	05/24/2002	Eric Samain	065691-0267	6242

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FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER

PROUTY, REBECCA E

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 12/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/019,954

Applicant(s)

SAMAIN ET AL.

Examiner

Rebecca E. Prouty

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 October 2005.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-24 and 26-46 is/are pending in the application.
- 4a) Of the above claim(s) 15-17, 21-24, 29, 31-38 and 40-46 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-14, 18-20, 26-28, 30, and 39 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____

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Claim 25 has been canceled. Claims 1-24 and 26-46 are still at issue and are present for examination.

Applicants' arguments filed on 10/05/05, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 15-17, 21-24, 29, 31-38, and 40-46 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention or species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 1/13/05.

Claim 7 is objected to because of the following informalities: the "and" in " α -1, **and** 4-fucosyl-transferase." At the end of the claim should be deleted. Appropriate correction is required.

Claims 2, 26, and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is confusing in the recitation "wherein said cell also comprises at least one gene encoding an enzyme capable of modifying an endogenous precursor, said enzyme being identical

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to or different than the enzyme of claim 1 as it is unclear if the gene being recited must be recombinantly introduced or if the claim is intended to include endogenously encoded genes. If the claim is broad enough to encompass endogenous genes it is not further limiting of claim 1 as every microorganism clearly encompasses endogenous genes which modify glycolytic pathway intermediates which are clearly precursors of all oligosaccharides. Furthermore the recitation of "enzyme of claim 1" is unclear as claim 1 recites a method not an enzyme. Furthermore it is not clear how the enzyme encoded could be the same as recited in claim 1 as then the claim clearly does not further limit claim 1 even if the gene is recombinantly supplied.

Claim 26 is incomplete as depending from claim 25. For purposes of further examination it is presumed this claim was intended to depend from claim 1.

Claim 30 is indefinite in the recitation of "glucose precursor" as the specification does not define the scope of this term. As glucose is the primary carbon source of almost all known microorganisms, the scope of compounds which could be considered "glucose precursors" is enormous and impossible to define without complete knowledge of all metabolic pathways present in a microorganism.

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Claim 30 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 30 as amended recites methods of producing lacto-N-neo-tetraose or polylactosamine wherein the "culturing occurs in the presence of a glucose precursor" The specification as originally filed fails to provide support for this limitation.

Claims 1-14, 18-20, 26-28, 30, and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is explained in the previous Office Action.

Applicants argue that the description of genes, precursors, and types of cells that can be used to practice the claimed invention is adequate in light of the knowledge of one of skill in the art as the specification provides lists of suitable

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genes, precursors, and types of cells, and specific examples of suitable genes, precursors, and types of cells. The examiner acknowledges that the specification provides lists of available genes and precursors as well as a list of several known microorganisms. However, providing lists of sources of each individual component is insufficient to provide an adequate written description of the methods recited in the claims as each gene cannot be used with each with every precursor in every microorganism for the synthesis of any desired oligosaccharides. Practicing the methods of the claims requires detailed knowledge of the biosynthetic pathways for the synthesis of any desired oligosaccharide, knowledge of the source of all enzymes necessary for such synthesis, knowledge of the metabolic/catabolic pathways present in the microorganism to be used and detailed knowledge of how these factors are interrelated such that one obtains the desired result. Oligosaccharides encompass an enormous family of highly complex compounds which are synthesized by highly complex biosynthetic pathways by an enormous number of different enzymes many of which are present in only a small number of microorganisms. Wild type *E. coli* produce only a very limited number of oligosaccharides while other microorganisms may produce different oligosaccharides by pathways that are only poorly

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defined in the art. Furthermore, while genes for the synthesis of some specific oligosaccharides are provided by the specification and/or prior art, use of any combination thereof for the production of any oligosaccharide is not a straightforward process involving only the transformation of a single gene into *E. coli* and expression of this gene therein. For many oligosaccharides to be produced multiple genes are necessary only some of which may be available in the prior art, the biosynthetic pathways as well as competing metabolic processes are not well defined, and all necessary precursors may not be present or may not be present in sufficient amounts. As such the specifications provision of a laundry list of known genes, precursors, and types of cells is insufficient to describe the breadth of the claimed methods.

Claims 1-14, 18-20, 25-28, 30, and 39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of making lacto-N-neotetraose or polylactosamine from lactose using Lac Z⁻ *E. coli* transformed with the *Neisseria gonorrhoeae* LgtA and LgtB genes, does not reasonably provide enablement for methods of making any oligosaccharide from any exogenous precursor in any bacterium. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected,

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to make and use the invention commensurate in scope with these claims. The rejection is explained in the previous Office Action.

Applicants arguments in response to the enablement rejection essentially repeat the same argument presented in response to the written description rejection. For all the reasons presented above, the mere provision of lists of available genes, precursors, and types of cells, as several specific working examples is insufficient to enable the enormously broad scope of the claimed methods as the available information barely scratches the surface of the knowledge which would be necessary to practice the scope of the claimed methods without undue experimentation. The synthesis of each distinct oligosaccharide in every different microorganism would present distinctly different issues which cannot be predicted from the success of the synthesis of other oligosaccharides in other microorganisms in view of the enormous diversity in the metabolic pathways of different microorganisms.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-14 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Bettler et al.

Bettler et al. teach the intracellular production of the oligosaccharide β Gal(1,4)[β GlcNAc(1,4)]₄GlcNAc using a LacZ⁻ *E. coli* transformed with the *Azorhizobium* NodC gene encoding chitin pentaose synthase and the *Neisseria gonorrhoeae* LgtB gene encoding an β -1,4-galactosyltransferase from exogenously provided glycerol using high cell density culture techniques as recited in claims 10-13 and that these culture techniques lead to high production levels of the desired oligosaccharide. As such Bettler et al. meets all limitations of the instant claims.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35

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U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 18-20, 27, 28, and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bettler et al. in view of Kozumi et al.

Bettler et al. is described above but do not specifically teach the use of lactose as precursor for the production of a desired oligosaccharide, the use of lactose permease for the transport of exogenous lactose into the cell, use of an inducer such as IPTG for increasing the expression of the glycosyltransferase and/or the expression of the lactose permease gene, or the production of a radioactively labeled oligosaccharide.

Kozumi et al. teach the production of the trisaccharide globotriose from lactose using a permeabilized LacZ⁻ *E. coli* transformed with the *Neisseria gonorrhoeae* LgtC gene encoding an α -1,4-galactosyltransferase (see page 848-849). However the lactose precursor of Kozumi et al. is not internalized into the cell as the cells of Kozumi have been detergent treated to destroy the cell membrane.

Bettler et al. clearly teach the advantages of production of a desired oligosaccharide intracellularly in a growing *E. coli* culture including that overproduction and purification of

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the glycosyltransferases is not needed, that the metabolic pathways for synthesis of most sugar-nucleotide donors is already present, the culture medium is inexpensive and fermenter technology is well established. Therefore, it would have been obvious to use the transformed LacZ⁻ *E. coli* of Kozumi et al. without permeabilizing the membrane as taught by Bettler et al. While this would clearly require the lactose precursor to be internalized, the *E. coli* Lac Y gene is well known in the art to encode the lactose permease necessary for active transport of lactose across the plasma membrane of *E. coli*. A skilled artisan would have been motivated to overexpresss this gene in the bacteria of Kozumi et al. as lactose is the precursor used by Kozumi et al. and the presence of an active lactose permease would provide higher intracellular levels of the precursor. A skilled artisan would reasonably expect that increasing the intracellular levels of the precursor would increase the amount of globotriose produced. Furthermore, while Kozumi et al. do not specifically teach the use of an inducer such as IPTG for increasing the expression of the glycosyltransferase and/or the expression of the lactose permease gene, the lactose promoter of *E. coli* is well known in the art to be induced by IPTG. As high levels of intracellular lactose are clearly necessary to produce high levels of globotriose, it would have been obvious to induce

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the expression of the lactose permease gene with IPTG in order to ensure high levels of the precursor intracellularly.

Bettler et al. and Kozumi et al. further do not specifically teach the production of radioactively labeled oligosaccharides. However, as the use of radioactively labeled oligosaccharides is well known in the art it would have been obvious to produce radioactively labeled globotriose by including radioactively labeled lactose or galactose (i.e., the precursors of the globotriose) in the reaction.

Claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bettler et al. in view of Kozumi et al. as applied to claims 18-20, 27, 28, and 39 above, and further in view of Johnson and Gotschlich (WO 96/10086).

Bettler et al. and Kozumi et al. are described above but does not teach the production of lacto-N-neotetraose from lactose using a bacterium transformed with a β -1,3-N-acetylglucosaminyltransferase and a β -1,4-galactosyltransferase gene. However, Bettler et al. clearly suggest the production of other oligosaccharides using as similar strategy to that used for β Gal(1,4)[β GlcNAc(1,4)]₄GlcNAc production in *E. coli* transformed with other bacterial glycosyltransferase genes (see page 211).

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Johnson et al. teach the production of lacto-N-neotetraose from lactose using bacterially expressed β -1,3-N-acetyl-glucosaminyltransferase and β -1,4-galactosyltransferase from *Neisseria gonorrhoeae* (see page 65).

Gotschlich teach the *Neisseria gonorrhoeae* LgtA and LgtB genes which encode the β -1,3-N-acetyl-glucosaminyltransferase and β -1,4-galactosyltransferase necessary for the synthesis of the lacto-N-neotetraose structures found on the lipooligosaccharides of the bacteria and the use of these proteins for the synthesis of lacto-N-neotetraose.

Therefore, it would have been obvious to produce lacto-N-neotetraose intracellularly in a LacZ⁻ *E. coli* transformed with the *Neisseria gonorrhoeae* LgtA and LgtB genes as Bettler et al. et al. clearly teach the usefulness of this system for the production of a variety of oligosaccharides, both Johnson and Gotschlich teach that lacto-N-neotetraose is a oligosaccharide of interest, Johnson show that this oligosaccharide can be produced using the β -1,3-N-acetyl-glucosaminyltransferase and β -1,4-galactosyltransferase from *Neisseria gonorrhoeae* and lactose as a precursor and Gotschlich teach the genes necessary for producing the transformed strain. While this would clearly require the lactose precursor to be internalized, the *E. coli*

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Lac Y gene is well known in the art to encode the lactose permease necessary for active transport of lactose across the plasma membrane of *E. coli*. A skilled artisan would have been motivated to overexpresss this gene in the bacteria as lactose is the precursor suggested by Johnson and the presence of an active lactose permease would provide higher intracellular levels of the precursor. A skilled artisan would reasonably expect that increasing the intracellular levels of the precursor would increase the amount of lacto-N-neotetraose produced.. Furthermore, as high levels of intracellular lactose are clearly necessary to produce high levels of lacto-N-neotetraose, it would have been obvious to induce the expression of the lactose permease gene with IPTG in order to ensure high levels of the precursor intracellularly.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca E. Prouty whose telephone number is 571-272-0937. The examiner can normally be reached on Tuesday-Friday from 8 AM to 5 PM. The examiner can also be reached on alternate Mondays

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system,

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see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A handwritten signature in black ink, appearing to read "Rebecca Prouty", with a stylized flourish extending from the end.

Rebecca Prouty
Primary Examiner
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